Remarks

Claims 1-7 are pending in the application. Claims 1 and 2 have been amended. Support for the new claims and claim amendments can be found throughout the application, including the claims as originally filed. For instance, support for the amendment to claims 1 and 2 can be found on page 18, lines 19-20 of the specification. Importantly, no new matter has been added to the claims. The amendment to the claims should not be construed to be an acquiescence to any of the rejections. The amendments to the claims are being made solely to put the claims in proper format to expedite the prosecution of the above-identified application. The Applicant reserves the right to further prosecute the same or similar claims in subsequent patent applications claiming the benefit of priority to the instant application. 35 USC § 120.

Response to Rejections under 35 U.S.C. § 103(a)

Claims 1-7 stand rejected under 35 U.S.C. § 103(a) based on the Examiner's contention that they are obvious over Kim et al. (U.S. Patent No. 5,723,147) or Kim et al. (Cancer Research, 1993, 53, 1596-1598) in view of either Gao (U.S. Patent No. 5,795,587) or Papahadjopoulos (U.S. Patent No. 6,071,533). The Applicants respectfully traverse this rejection.

Applicants submit that either Kim et al. reference in view of either Gao or Papahadjopoulos do not render claims 1-7 obvious because the preparation steps disclosed in the Kim et al. references are not the same as the claimed methods. The different methods result in different liposomal complexes. The Kim et al. references disclose multivesicular DepoFoam which is made up of large liposomes for drug depot, and the present invention discloses a preparation for unilamellar liposome complexes which are smaller and more useful for transfer across the cell membrane.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

The Kim et al. et al. references both disclose a method of preparing multivesicular

liposome complexes comprising a biologically active substance. *See* the title of U.S. Patent No. 5,723,147 and throughout, and the Cancer Research paper, paragraph 2, line 1, and throughout. These are prepared in a different manner than the claimed methods. Multivesicular liposomal complexes by definition are not unilamellar. Multivesicular liposomal complexes comprise inner non-concentric chambers enclosed by lipid bilayers. They are relatively large complexes and not the unilamellar liposomes of the present methods where there is one continuous lipid bilayer.

In the U.S. Patent No. 5,723,147 Kim et al. reference, the lipid-bioactive agent emulsion of chloroform and water is added to an aqueous solution of glucose and lysine, which the examiner contends is a complexing agent. See column 8, lines 35-39, under Example 1; see also column 8, lines 43-47, under Example 1, where step 5) begins "[t]o obtain the multivesicular liposomes..."

In the Cancer Research Kim et al. reference, the multivesicular liposomes are prepared in the same manner. See page 1596, second column, under "Synthesis of Depo/Ara-C." Applicants point out that the lysine used is free-base lysine which is non ionic and would not act as a complexing agent. This supports Applicants' contention, made previously, that the Kim et al. references do not disclose a complexing agent.

Contrast these methods to the presently claimed methods where an aqueous suspension of the complexing agent is added to the lipid-bioactive agent/water-organic solvent emulsion, as opposed to the reverse: the emulsion being added to the aqueous lysine solution of the Kim et al. references. Applicants caution the Examiner not to view this as a trivial difference. The formation of liposomes from lipids is dependent on physical chemistry, in particular, the potentials between the hydrophilic and hydrophobic ends of the lipid and their environment. Adding one suspension of a certain composition to another suspension of different composition will not necessarily produce the same results if the order is switched.

Gao and Papahadjopoulos were cited by the Examiner as teaching that polycations stabilize nucleic acids, but neither reference makes up for the deficient teachings of the Kim references for not teaching unilamellar liposomes.

Accordingly, the Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. § 103(a).

Fees

The Applicants believe they have provided for the required fees in connection with the filing of this paper. Nevertheless, the Director is hereby authorized to charge any additional required fee to our Deposit Account, **06-1448**.

Conclusion

For the foregoing reasons, the Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the pending claims are now in condition for allowance and early notification to this effect is earnestly solicited. If any questions are raised by this Amendment and Response, the Examiner is urged to contact the undersigned at the telephone number listed below.

Respectfully submitted,
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